Cardiac amyloidosis: The starched heart

Assuero Giorgetti, MD,[a] Dario Genovesi, MD,[a] and Michele Emdin, MD, PhD[a,b]

[a] Fondazione CNR/Regione Toscana "Gabriele Monasterio", Pisa, Italy
[b] Institute of Life Sciences, Scuola Superiore Sant'Anna, Pisa, Italy

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Rudolf Ludwig Carl Virchow (1821-1902), named ''the Pope of Medicine'' by his contemporaries, has been one of the most influential figures in the history of medicine, first establishing the modern pathology. However, he was not immune to mistakes, as it was the case for his interpretation of the remnants of the Neanderthal man. In 1872, Virchow was called to express his eminent opinion about fossil bones discovered 16 years before in the Neander valley. As a convinced opponent of Darwin's theory of evolution, he stated that the Neanderthal had not been a primitive human, but a homo sapiens affected by arthritis and rickets. Some years before this story, he had observed strange extracellular deposits of amorphous material, similar to starch (latin: amilum) and that he wrongly interpreted as a polysaccharide.[1] Since that observation, we refer to a heterogeneous group of diseases characterized by the common future of extracellular depositions of insoluble fibrillar misfolded proteins, with the term amyloidosis. This systemic disease may involve multiple organs and, not infrequently the heart is the target of amyloid, determining, by interstitial accumulation and toxic effects on cardiomyocyte, cell apoptosis, necrosis, and disjunction, as well as pseudohypertrophy, tissue stiffness, biventricular diastolic and systolic dysfunction, leading, ultimately, to the phenotype of overt heart failure, characterized by morbidity and mortality. CA is not a rare disease: light-chain-related CA (AL) has an estimated incidence between 3 and 14 cases per million persons per year, and a prevalence of 30,000 to 45,000 patients in the United States and European countries.[2-4] Conversely, autopsy in patients $\geq$ 75 years old with heart failure with preserved ejection fraction found transthyretin-related CA (ATTR-wild type, senile amyloidosis) in 32%,[5] most misdiagnosed. Cardiologists are the gatekeepers for the patients with suspected amyloidosis, but the correct diagnosis is made in less than 20% of the cases.[6] This may happen because signs and symptoms of the disease are not specific (dyspnea, edema), and because of the widespread misconceptions about the nature, epidemiology, clinical characteristics, classification, and diagnostic and therapeutic work-up in the different types of the disease (''it's a rare disease,'' ''diagnosis can be achieved only by invasive procedures such as myocardial biopsy and only in specialized centers''). For all these reasons and for a diffuse, wrong belief about the lack of effective therapies and irreversible fatal outcome, a nihilistic attitude is widely present towards the disease. As a consequence, a large number of patients are diagnosed when end-stage heart failure prevents the efficacy of therapeutic interventions. Therefore, an early and correct diagnosis is crucial to ameliorate the outcome of this disease, which is definitely not rare and whose outcome may improve after appropriate treatment.

The coexistence of even slight (pseudo)hypertrophy and worsening left ventricular diastolic dysfunction with dyspnea on effort and/or edema or, even in absence of symptoms and signs of heart failure, with increased plasma level of B-type natriuretic peptide (namely, N-terminal fragment of pro BNP, NT-proBNP) and (high sensitivity) troponin T or I, with (in AL CA) low QRS complex voltages at the electrocardiogram should always raise the suspicion of CA, with younger age indicating a higher probability of AL CA or familial TTR CA, and older age indicating the probability of senile amyloidosis, which nevertheless may occur rarely along with AL CA as a''dual'' pathology. This may or may not occur in presence of multi-organ involvement, requiring a multi-specialist approach to the disease management; cardiologists then must be guided—and

Reprint requests: Assuero Giorgetti, MD, Fondazione CNR/Regione Toscana Gabriele Monasterio, Via G. Moruzzi 1, 56124, Pisa, Italy; *asso@ftgm.it*

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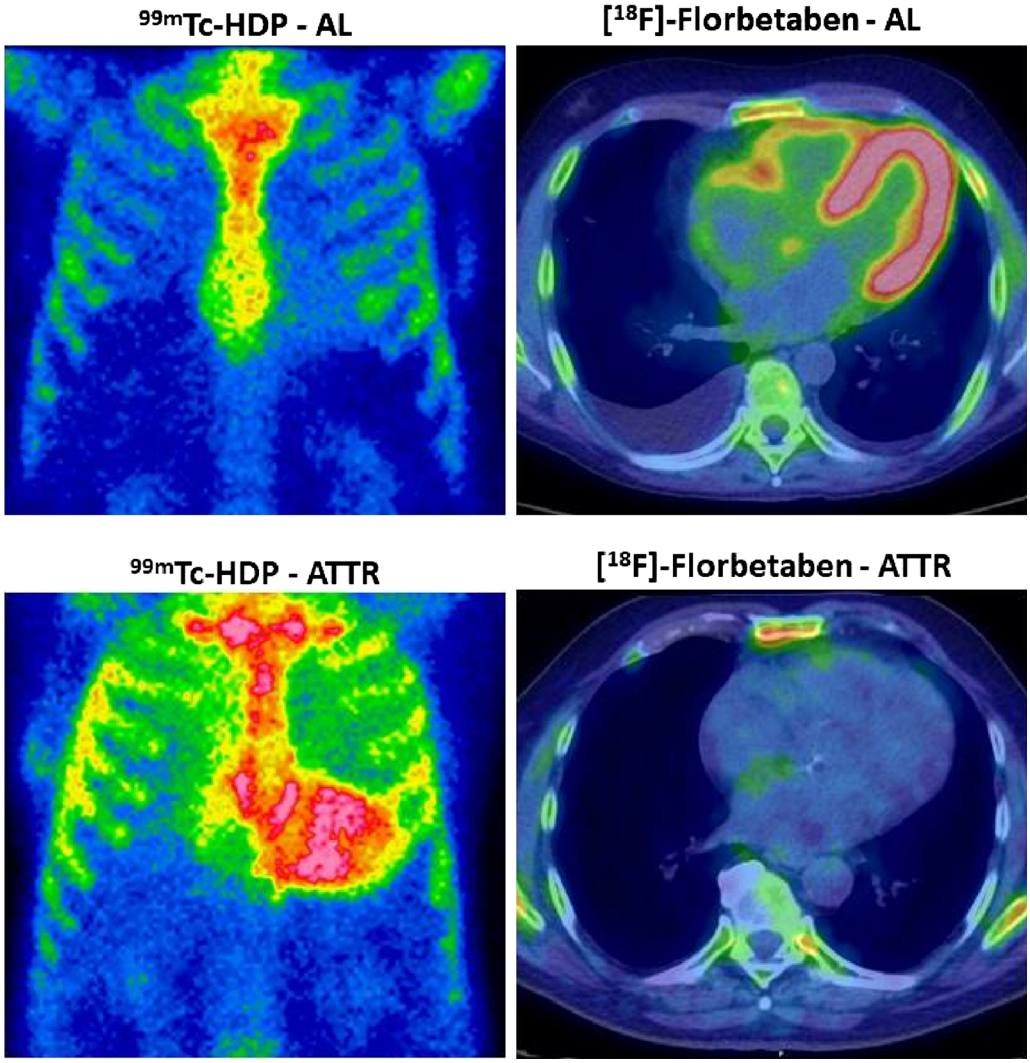

Figure 1. Nuclear imaging in patients with endomyocardial biopsy proven cardiac amyloidosis. Above, bone scintigraphy (left) and PET imaging (right) in a patient with AL CA: bone scan does not show significant myocardial uptake of ^{99m}Tc-HDP while PET imaging (^{18}F-Florbetaben) is markedly positive. Below, nuclear imaging in a patient with ATTR CA: there is a diametrical opposite scenario with a markedly positive bone scintigraphy (Perugini scale: 4) and absent myocardial uptake of PET radiotracer.

guide—hematologists, neurologists, nephrologists, and specialists of cardiac imaging (ultrasound, nuclear medicine, and magnetic resonance experts). Additional clues may support the diagnosis of CA, as the history of carpal tunnel syndrome in ATTR, particularly if bilateral and in males,[7] of spontaneous rupture of biceps tendon, neuropathic pain, orthostatic hypotension, and a diagnosis of ''hypertrophic cardiomyopathy'' in the elderly. The association of hepatomegaly, proteinuria, and heart failure should trigger consideration of the diagnosis of AL CA, in which macroglossia may be observed. Even recently the definitive diagnosis remained a challenge, possible only after endomyocardial biopsy. This contributed to discourage the physician in charge of the patient, as the technique is restricted to a few referral centers and requires skills in both the execution of the exam and the analysis of samples. Complications of biopsy are rare but when they occur may be life-threatening. As a consequence, in the recent years many efforts have been made to exploit non-invasive approaches. As reported, cardiac biomarkers can be used for diagnosis, patient management, and prognostication. Elevation in BNP/NT-proBNP reflects myocardial stretch exerted by the amyloid deposits, whereas

elevation in cardiac troponin is thought to represent myocyte damage. As recently demonstrated, high NT-proBNP, low cardiac output, and pericardial effusion at the time of screening should prompt physician to refer the patients to amyloidosis referral center.[8] Another promising biomarker for prognostic stratification is adrenomedullin.[9] Myocardial imaging is of fundamental value to validate the suspicion of the disease, to evaluate therapy response and to predict patient's outcome. Echocardiography and cardiac magnetic resonance imaging (cMRI) are essential tools in the CA patient management. A ''brilliant'' thickened left ventricle at echocardiography, with small chamber volume, valve thickening, atrial enlargement, and signs of elevated filling pressures, with a restrictive diastolic pattern should alarm the cardiologist. Two-dimensional strain mapping with relative preservation of apical function, that can be represented in a typical bull's eye picture, is rare in other cardiomyopathies.[10] cMRI can provide tissue characterization, precise measurements of wall thickness, and cardiac chamber volumes, accurate evaluation of heart function. As amyloidosis is characterized by deposition of misfolded proteins and expansion of extracellular volume, detectable by t-1 mapping, late enhancement gadolinium imaging is highly suggestive of amyloidosis.[11,12] Echocardiography and cMRI are undoubtedly useful techniques for the early identification of cardiac hypertrophy and for the non-invasive monitoring of the disease. However, the specificity of ultrasounds is low, and cMRI is not suitable in up to 20% of patients (claustrophobia, older pace-maker implantation, renal insufficiency may prevent the exam). With these techniques, the information provided is not based on the direct demonstration of amyloid fibrils and they often fail in the recognition of CA subtype.

In the past decades, radionuclide molecular imaging has scored a fantastic goal against CA. As students of nuclear medicine, we remember the occasional finding of heart uptake in bone scintigraphy, usually in elderly male patients. At that time, we did not know its meaning, usually attributed to a possible consequence of a post-ischemic myocardial injury. Now we know that a myocardial damage is present but is not linked to myocardial ischemia: it is the ''starched heart''! Perugini and colleagues demonstrated that a high heart retention of ^{99m}Tc-DPD had a very high diagnostic accuracy in the recognition of patients with ATTR CA.[13] Recently, Gillmore and co-workers investigated 1217 patients with suspected cardiac amyloidosis who were referred for bone scintigraphy using the 3 available ^{99m}Tc-labeled bone-seeking agents (^{99m}Tc-DPD, ^{99m}Tc-HMDP, and ^{99m}Tc-PYP).[14] This study demonstrated a comparable diagnostic performance of the different radiotracers for the detection of ATTR CA. Moreover, the authors suggested that, in patients with heart failure symptoms, with imaging findings of myocardial hypertrophy and without detectable monoclonal proteins, bone scintigraphy could establish the diagnosis of ATTR CA. In other words, we can make a definitive diagnosis without the need for histology and with a degree of certainty hardly achieved by other non-invasive modalities. Despite this success, bone-seeking radiotracers are not amyloid-specific and a calcium-mediated mechanism has been suggested, though not completely demonstrated.[15]

More recently, nuclear radiopharmacy has expanded its armamentarium with amyloid-specific probes. ^{11}C-Pittsburgh compound-(PiB)[16] and ^{18}F-Flutemetamol[17] are benzothiazoles while ^{18}F-florbetaben[18] and ^{18}F-florbetapir[19] are stilbene derivatives with a very similar structure. These radiotracers bind to β-amyloid plaques and they have been developed for positron emission tomography (PET) imaging of neurodegenerative disorders. Despite this exclusive clinical indication for Alzheimer disease diagnosis, an increased interest has merged as possible probes for CA. In preliminary studies, these radiotracers have demonstrated myocardial retention in patients with proven CA while the uptake is not present in patients without the disease.[18,20,21] Moreover, contrary to bone-seeking agents, PET radiotracers seem to be the first to specifically image AL CA, with a high target-to-background ratio, with the potential to quantify amyloid burden and response to therapy. In this number of the Journal of Nuclear Cardiology, Kim and co-workers performed a systematic review and meta-analysis on the diagnostic performance of PET with amyloid probes in CA.[22] The authors concluded that PET has a very high diagnostic accuracy and quantitative measures can improve the early assessment of cardiac amyloid burden and the identification of type-specific CA. The paper has some limitations. First, the limited number of the available studies, totalizing less than 100 patients included in the analysis. Second, various quantitative/semi-quantitative approaches have been used in the included studies (retention index, target-to-background ratio, SUV, compartmental analysis). Maybe all these approaches are useful but, at moment, we do not know which have the best clinical performance. We do not know which parameter can best reflect the myocardial burden of CA or if a dynamic analysis can aid the identification of specific-type CA. Anyway, the work of Kim and al. has the merit to focalize clinician's attention on this new opportunity. PET imaging has the potentiality to further reduce the need of histological confirmation of CA. In high clinical suspicion of CA, an early dual isotopes nuclear procedure (bone scintigraphy/PET imaging, at

least in some instances) could solve the diagnostic issue and the recognition of disease subtype (Figure 1). As repeatedly stated, early diagnosis and specific therapeutic intervention are the only weapons to improve the prognosis of these patients. Specific treatments (chemotherapy or stem cell transplantation for AL, RNA-silencing molecules, or stabilizers for ATTR) can reduce the myocardial burden or block new deposition of amyloid fibrils. PET imaging with amyloid probes has the potentiality to trace these molecular processes over time. From this point of view, an interesting perspective concerns the futuristic use of PET/cMRI as a one-stop shop imaging in CA. Finally, the results of the present meta-analysis reinforce the need for the expansion of indications for the use of these radiopharmaceuticals, registered in many countries only for brain studies.

From the time of Virchow, the starched heart continues to be an evolving concept.

Disclosure

None of the authors have anything to declare.

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